77. The method of claim 51, wherein said exogenous sequence is flanked at its 5' and 3' ends by FRT DNA elements, and wherein stop codons have been inserted 3' to the selectable marker for each of the three reading frames for the porcine α-1,3 galactosyltransferase gene.--

REMARKS

Status of the Claims

Claims 1-3, 46-51, 67, and 70-77 are pending in this application, claims 68 and 69 having been cancelled and claims 74-77 having been added by the above amendments.

Claim 1 has been amended as follows. Element (1) now specifies the coding region (nucleotides 91-1203) within SEQ ID NO:7 rather than full length SEQ ID NO:7. Support for this amendment is SEQ ID NO:7 as depicted in the Sequence Listing. Element (2) has been amended to specify "a sequence encoding a porcine polypeptide having α-1,3 galactosyltransferase activity and having the amino acid sequence of SEQ ID NO:10." Support for this amendment is prior element (3) of the claim and SEQ ID NO:10 as depicted in the Sequence Listing. The clause " a sequence that hybridizes with a sequence . . . 0.5 x SSC" in element (3) has been deleted and replaced with a clause specifying "a sequence that encodes a second polypeptide identical to said porcine polypeptide except for one or more conservative amino acid substitutions, wherein said second polypeptide retains a functional α-1,3 galactosyltransferase catalytic site, a functional membrane anchor domain and a functional stem region." Support in the specification for this amendment is on page 6, line 21 to page 7, line 3; Applicants submit that one of ordinary skill in the art would understand "minor amino acid variations" (as recited in the cited text from the specification) to be equivalent to "conservative amino acid substitutions," the latter being a more commonly used term of art.

Claim 46 has been amended to specify that the gene in the claimed construct, prior to disruption, encodes a α-1,3 galactosyltransferase with an amino acid sequence of SEQ ID NO:10. This amendment is supported by the specification, e.g., at page 7, line 24 to page 5, line 5, and Example 7. Claim 51 has been amended to specify that in the construct used in the claimed method is the construct specified by claim 46; prior to amendment, claim 51, instead of referring back to claim 46, repeated the relevant language of claim 46. Claim 67 has been

amended to specify that, as in claim 46, the gene (in the claimed cell), prior to disruption, encodes the α-1,3 galactosyltransferase with an amino acid sequence of SEQ ID NO:10. In addition, claim 69 has been cancelled and the limitation specified by it has been added to claim 67. Support for these amendments is the same as that recited above for the amendment to claim 46. Claims 69-73 have been amended in response to the 35 U.S.C. §112, paragraph 2, rejection by correcting their dependencies (see below).

New claims 74-77 are supported by the specification, e.g., at page 31, line 26 to page 36, line 24.

Priority of SEQ ID NO:7

In regard to the comments on page 2, paragraph 2, of the Office Action, Applicants respectfully submit that, for the purposes of 35 U.S.C. §102(e), the date of "invention" for SEQ ID NO:7 was prior to October 16, 1995, the date the corrected SEQ ID NO:7 was submitted in an Information Disclosure Statement in the parent case (U.S. Application No. 08/378,617, now U.S. Patent No. 5,849,991). Thus, the latest possible priority date for the correct SEQ ID NO:7 is October 16, 1995, and not December 4, 1997 (the filing date of the instant application), the date asserted by the Examiner to be the "effective filing date of the polynucleotide sequence of SEQ ID No. 7."

35 U.S.C. §112, second paragraph, comments

In response to the Examiner's comments on page 1, last paragraph, and page 2, first paragraph, Applicants have amended claims 70-73 by correcting their dependencies and have thereby provided the appropriate antecedent bases for the claims.

35 U.S.C. §102(e) rejection

Claims 1-3 and 68 stand rejected under 35 U.S.C. §102(e) as being clearly anticipated by Sandrin et al. 1998, U.S. Patent No. No. 5,821,117.

Claim 68 is cancelled. Applicants do not understand the first full sentence on page 4 ("Sandrin et al. . . . (e.g. column 9, 10)") of the Office Action. Nevertheless, Applicants

understand the Examiner's position to be that the Sandrin et al. reference anticipates claims 1-3 and 68 by disclosing: (a) a sequence (SEQ ID NO:2) that would be capable of hybridizing to SEQ ID NO:7 of the instant application under high stringency conditions; (b) the amino acid sequence of the polypeptide encoded by the polynucleotide with SEQ ID NO:2; and (c) transfection of COS cells with cDNA encoding the polypeptide. Applicants submit that the claims as amended are not anticipated by Sandrin et al. because, in the coding region of the Sandrin et al. SEQ ID NO:2, codon 215 encodes an isoleucine residue while the corresponding codon (227) in SEQ ID NO:7 of the instant application encodes a methionine residue. Thus neither the nucleic acid molecule of claim 1, the host cell of claim 2, nor the α-1,3 galactosyltransferase of claim 3 are anticipated by the disclosure of Sandrin et al. Applicants also draw the Examiner's attention to the fact that, while not required to distinguish claims 1-3 of the present invention from the disclosure of Sandrin et al., (a) codon 27 of the Sandrin et al. SEQ ID NO:2 encodes an arginine residue while in the coding region of SEQ ID NO:7 of the instant application codon 27 encodes a serine residue, and (b) codons 28-39 of SEQ ID NO:7 of the instant application are absent from the Sandrin et al. SEQ ID NO:2.

In light of the above considerations, Applicants request withdrawal of the rejection under 35 U.S.C. §102(e).

35 U.S.C. §103(a) rejections

(a) Claims 46, 47, 67, 69, and 70 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sandrin et al., U.S. Patent No. 5, 821,117.

Claim 69 is cancelled and the limitation specified by it has been added to claim 67. Amended claims 46 and 67 require that the disrupted gene, prior to disruption, encode a α-1,3 galactosyltransferase with an amino acid sequence of SEQ ID NO:10. As pointed out above, Sandrin et al. discloses a porcine α-1,3 galactosyltransferase gene encoding a polypeptide with SEQ ID NO:2 (as assigned in Sandrin et al.), a sequence quite different from that disclosed in the instant application (SEQ ID NO:10). Thus, it could not have been obvious to one of ordinary skill in the art reading the Sandrin et al. reference to disrupt a gene encoding the α-1,3 galactosyltransferase with an amino acid sequence of SEQ ID NO:10 by insertion of an

exogenous sequence into the gene. Moreover, even if such an artisan did insert an exogenous sequence into a gene encoding the polypeptide disclosed by Sandrin et al., she would obtain a construct qualitatively different from that specified by claim 46. In addition, a porcine cell containing such a disrupted α-1,3 galactosyltransferase gene would similarly be qualitatively different from the porcine cell specified by claim 67.

(b) Claims 46-51, 67, 69-73 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sandrin et al., U.S. Patent No. 5, 821,117 and Galili, 1993 in view of Hodges et al. 1996, U.S. Patent No. 5,527,695.

Amended claims 46 and 67 require that the disrupted gene, prior to disruption, encode a porcine α-1,3 galactosyltransferase with an amino acid sequence of SEQ ID NO:10 . As argued above, Sandrin et al. does not disclose a gene encoding such a polypeptide and thus cannot render obvious the construct specified by claim 46 nor the porcine cell specified by claim 67. These defects in Sandrin et al are not remedied by the disclosures of either Galili et al. which merely suggests that "non primate donors which are genetically engineered to to lack α1,3GT activity . . . may be achieved by gene knockout technology" (page 481, column 1, second full paragraph) or Hodges et al. which teaches generally the technology of DNA constructs containing a FRT site (e.g., column 5, line 33 to column 6, line 17), various maize protein coding sequences (Examples 1-4), and a selectable marker gene (Example 3) without any reference to any α-1,3 galactosyltransferase coding sequence, let alone a porcine polynucleotide encoding an α-1,3 galactosyltransferase with an amino acid sequence of SEQ ID NO:10 . In view of these considerations, neither the DNA constructs of claims 46-50, the method of claim 50, nor the porcine cells of claims 67-73 are rendered obvious by the cited references when considered singly or in combination.

In light of these considerations, Applicants request withdrawal of the rejections under 35 U.S.C. §103(a).

CONCLUSION

Applicants submit that claims 1-3, 46-51, 67, and 70-77 patentably define the invention. Applicants request that the Examiner reconsider the rejections set forth in the Office Action, and permit the pending claims to pass to allowance.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicants' undersigned representative can be reached at the telephone number listed below.

Enclosed is a check in payment of the fee for the two-month extension of time. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 8/14/00

Stuart Macphail

Stuart Macphail, Ph.D.
Reg. No. 44,217

Fish & Richardson P.C.
45 Rockefeller Plaza, Suite 2800
New York, NY 10111
Telephone: (212) 765-5070
Facsimile: (212) 258-2291
30020771.doc